HEPATOCYTE GROWTH FACTOR GENE DELIVERED INTRAMYOCARDIALLY IMPROVES CARDIAC FUNCTION AND STRAIN ON MR IMAGING

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INTRODUCTION: Treatment of ischemic heart disease remains a worldwide problem. Gene therapy and cell transplantation have made desirable progress. Hepatocyte growth factor (HGF) is an angiogenic, antifibrotic and anti-apoptic agent, detected in patients serum after myocardial infarction and associated with decreased LV dilatation. Plasmid HGF gene expressing two isoforms of HGF has been recently developed but not tested in infarcted myocardium.

PURPOSE: To determine the effects of intramyocardial HGF gene therapy transferred by plasmid DNA on left ventricular function and strain of infarcted myocardium using MR imaging.

MATERIALS AND METHODS: Myocardial infarction was created by occlusion of the LAD coronary artery for two hours followed by reperfusion in 16 pigs. In 8 pigs a plasmid expressing two isoforms of HGF (VM202, Viromed Co. Ltd, Korea) was injected 2hr after reperfusion into 8 sites (4 in infarcted and 4 in periinfarcted myocardium). The remaining 8 pigs served as controls. MR images were acquired 3 days and 7-8 weeks after infarction. Short axis cine MR images covering the whole left ventricle were acquired using 1) steady state free precession: α=70°, TE=1.8 ms, TR=3.6 ms, Image resolution=1x1x10 mm, no slice gap, retrospective ECG-triggering with 16 time phases) and 2) tagging MRI (CSPAMM, α=25°, TE=6 ms, TR=37 ms, Image resolution=1x1x10 mm, no slice gap, prospective triggering with 18 heart phases) using a 1.5 T Philips Intera. Circumferential strain and systolic wall thickening were analyzed by the HARP software and Segment in three slices. Histochemical and histopathology stains were used to size myocardial infarction, determine vascular density and myocardial viability.

RESULTS: At the global level, the ejection fraction (EF) and infarction size did not differ between control and treated animals at day 3 post infarction (p=0.57) (**Fig. 1**). HGF gene improved the ejection fraction and significantly reduced infarction size compared to control animals at 7-8 weeks. LV remodeling was observed in control animals, as reflected by the increase in LV volumes and decrease in ejection fraction (**Fig. 1**). At the regional level, circumferential strain in infarcted and peri-infarcted regions of treated animals was higher at 7-8 weeks than control animals (**Fig. 2**).

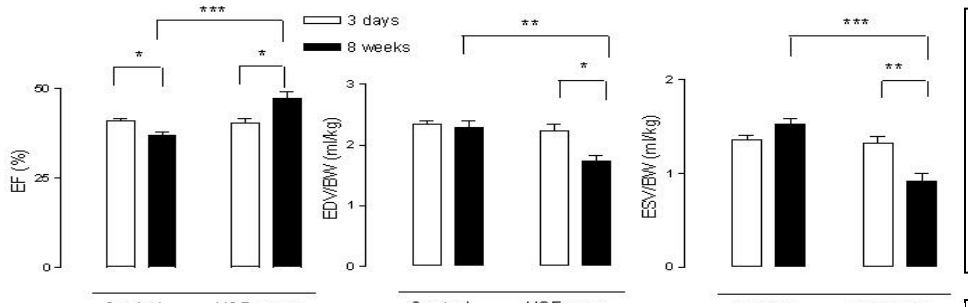

Fig. 1. Temporal evolution in ejection fraction (left), end-diastolic (center) and end-systolic volumes in control and HGF gene treated animals. At 7-8 weeks, treated animals showed improvement in the above parameters compared with control animals. Control animals developed LV remodeling.

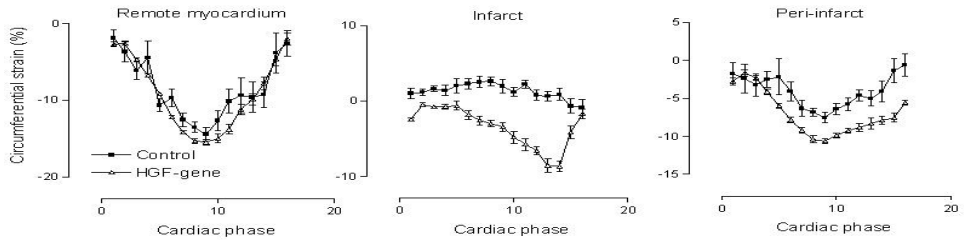

Fig. 2. Changes in circumferential strain of peri-infarcted, infarcted and remote myocardium during cardiac cycle at 7-8 weeks in control and treated animals. Circumferential strain in the peri-infarcted and infarcted myocardium is greater in treated than control animals.

Furthermore, systolic wall thickening also improved in the infarcted and peri-infarcted regions of treated animals (**Fig. 3**). Improvement in regional and global LV function is most likely attributed to the neovascularization and formation of peninsula/islands of viable myocardium in the peri-infarction zone as shown on histopathology.

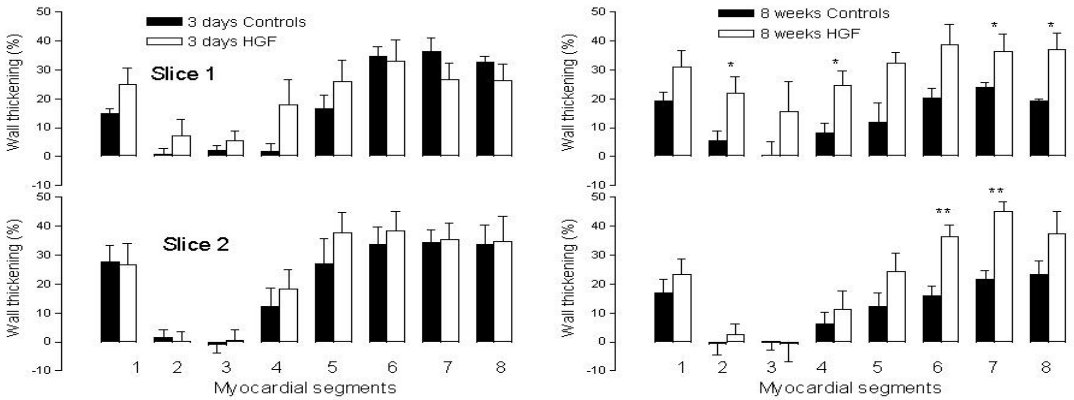

Fig. 3. Systolic wall thickening (mean±SEM) at 3 days (left) and at 8 weeks (right) for control animals (black bars) and treated animals (white bars). * p<0.05, ** p<0.01 in treated animals compared to controls.

CONCLUSION Intramyocardial injection of plasmid expressing HGF improved the ejection fraction, decreased LV volumes and prevented LV remodeling associated with infarction. It also increased regional strain in both peri-infarcted and infarcted regions. HGF gene results in the prevention of progressive heart dysfunction after myocardial infarction

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